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THE PATENTS ACT, 1970.

It is hereby Certified that annexed hereto is a True Copy of the Application on Form-1A and the Complete Specifcation filed on 6-3-1998 in connection with the Patent Application No 465/MAS/98 filed by Messrs Astra AB, a Swedish Company at S-151 85, Sodertalje, Sweden.----------

---------- In witness thereof I have hereunto set my hand

Dated this the 7th day of December, 1998.
16th day of Agrahayana, 1920, (SAKA).

S. Chandrasekaran

(S. Chandrasekaran),
DEPUTY CONTROLLER OF PATENTS & DESIGNS.

Patent Office Branch,
CHENNAI.

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

THE PATENTS ACT 1970

FORM 1A

APPLICATION FOR PATENT

By the assignee or legal representative of the true and first inventor

(See section 7)

We **M/S ASTRA AB, A SWEDISH COMPANY, AT S-151 85, SODERTALJE, SWEDEN**

hereby declare :-

(1) that we are in possession of an invention for

New Use

(2) that we claim to be the assignee(s) of or the legal representative (s) of **Mr. JanakiRaman Ramachandran, an American citizen at Survey No. 38, Farm House (Behind Vinayaka Layout), Puttenahalli, Yelahanka, Bangalore 560 064, Karnataka State, India**

who claim(s) and is/are believed to be the true and first inventor(s) thereof :

(3) that the provisional/complete specification filed with this application is (and the complete specification) and any amended specification which may hereafter be filed in this behalf will be true of the invention to which this application relates :

(4) that I/we believe that I am/we are entitled to a patent for the said invention having regard to the provisions of The Patents Act 1970 :

(5) that to the best of my/our knowledge information and belief, the facts and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application. I/We request that a patent may be granted to me/us for the said invention.

I/we request that all notices, requisitions and communications relating to this application may be sent to **M/s A.V. Nathan Associates, Patent & Trade Mark Attorneys Copy Right & Design, 451, 2nd cross, 3rd Block, 3rd Stage, Basaveshwara Nagar, Bangalore-560079. India.**

Dated this 2ND DAY OF JANUARY, 1999.

(MRS. A.V. NATHAN)
AGENT FOR THE APPLICANT.

To,
The Controller Of Patents,
The Patent Office, MADRAS.

ENDORSEMENT BY THE TRUE AND FIRST INVENTORS

I/We

Mr. JanakiRaman Ramachandran, an American citizen at Survey No. 38, Farm House, (Behind Vinayaka Layout), Puttenahalli, Yelahanka, Bangalore 560 064, Karnataka State India.

referred to on the reverse of this application as claiming to be the true and first inventor(s) hereby declare that the applicant(s) who has/have signed this application on the reverse is/are my/our assignee(s).

Dated this 2ND DAY OF JANUARY, 1999.

J Ramachandran

JanakiRaman Ramachandran

Two Witness :

1. M.A.MUKUND

ASTRA BIOCHEMICALS PRIVATE LIMITED
REGD. OFFICE : NO.6, 6TH MAIN
NEAR SRS ROAD, PEENYA
BANGALORE - 560 058

2.

(H.N. JAGANNATHA)

ASTRA BIOCHEMICALS PRIVATE LIMITED
REGD. OFFICE : NO.6, 6TH MAIN
NEAR SRS ROAD, PEENYA
BANGALORE - 560 058

THE PATENTS ACT, 1970
FORM 1A

APPLICATION FOR PATENT
By the Assignee or legal Representative of the True and First Inventor.
(See Section 7)

(To be made in triplicate and shall be accompanied by three copies of the provisional specification in Form 3, or the complete specification in Form 3A)

I/WE M/s. ASTRA AB, A SWEDISH COMPANY, AT S-151 85, SODERTALJE, SWEDAN.

hereby declare :-

(i) that I am/we are in possession of an invention for

" NOVEL PROCESS ".

(ii) that I/We/the said
claim(s) to be the assignee(s) of or the legal representative(s) of
MR. MILIND VASANTH RANGAISHENIV, AN INDIAN CITIZEN, AT 246, BEML LAYOUT, 11TH CROSS, 5TH MAIN, BASAVESHWARANAGAR, BANGALORE - 560 079, KARNATAKA STATE.

who claim(s) and is/are believed to be the true and first inventor(s) thereof;

(iii) that the provisional/complete specification filed with this application is (and the complete specification) and any amended specification which may hereafter be filed in this behalf will be, true of the invention to which this application relates;

(iv) that I/We believe that I am/we are entitled to a patent for the said invention having regard to the provisions of the Patents Act, 1970;

(v) that to the best of my/our knowledge, information and belief, the facts and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application. I/We request that a patent may be granted to me/us for the said invention.

I/We request that all notices, requisitions and communications relating to this application may be sent to MRS.A.V. NATHAN, at 451, 2nd Cross, 3rd Block, 3rd Stage, Basaveswaranagar, BANGALORE-560 079, KARNATAKA STATE, INDIA.

Dated this 5TH day of MARCH, 1987.

(MRS. A.V.NATHAN).
AGENT FOR THE APPLICANT

To

The Controller of Patents,
The Patents office,
MADRAS.

NOVEL PROCESS

The present invention relates to novel process for the preparation of prostaglandin compounds which are useful as medicaments.

Prostaglandins (PGs) are a family of 20-carbon fatty acids found in virtually all mammalian cells and are biosynthesised from C-20 polyunsaturated fatty acids *via* cyclooxygenase enzyme system (S. Bergstroem., *Science,* **157**, 382, 1967). For several decades, PGs have been the focus of extensive efforts in synthetic chemistry. Because of the potential therapeutic advantages, increasing attention is being focused on PG analogs. The nonavailability of suitable natural source coupled with their potential drug utility has led to the clinical development of a number of synthetic PG analogs. Among them, particularly interesting, both pharmacologically and clinically, are analogs incorporating methyl groups into the prostaglandin skeleton at C-15 (a). E. Yankee *et al., J. Amer. Chem. Soc.*, **96,** 5865, 1974) b) E. Yankee *et al., J. Amer. Chem. Soc.*, **94**, 3651, 1972). c). E. Yankee et *al., J. Amer. Chem. Soc.*, **96,** 5875, 1964) and references cited therein). The most rapid mode of metabolism (deactivation) of the natural PGs in man bas been shown to be the oxidation of the allylic C-15 alcohol, followed by very rapid reduction of the 13-14 double bond. The enzyme responsible for the oxidation, 15-hydroxy prostaglandin dehydrogenase has been isolated from a variety of tissue preparations (B. Samuellson *et al., Advanc. Biosci.*, **9,** 7, 1973).

Of particular interest is the 15-methyl $PGF_2\alpha$ (carboprost, Upjohn). Carboprost is clinically listed for treatment of post partum haemorrage as an alternative to methylergometrine or where the latter has produced inadequate response. Intramuscular injection of 250 mg of carboprost in sterile aqueous solution is the best therapy now available, very successful in cases ready for uterectomy due to bleeding not stoppcd by methergin etc. This has been registered for this indication in Sweden and India (available under the brand names Prostinefem in Sweden and Prosodin in India).

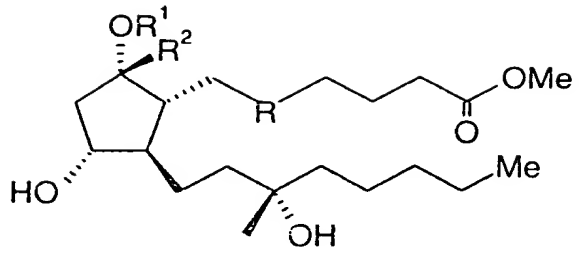
The development of a total synthetic route for carboprost is highly desirable because of its promising clinical potential. A large number of strategies towards the synthesis of PGs have been reported (E.J. Corey *et al., J. Amer. Chem. Soc.*, **90,** 3245 and 3247, 1968). However, known synthetic procedures often involve a multistep linear synthesis approach leading to high cost and a low overall yield of the final product. Noyori *et al* reported a convergent three-component coupling process, wherein the entire carbon framework is

assembled stereoselectively by tandem alkylation of an appropriate optically active enone (R. Noyori *et al., Angew. Chem. Int. Edn.(Eng.).*, **23,** 847, 1984 and references cited therein). The prostaglandin PGE_2 has also been synthesised using solid phase chemistry (S Chen, IBC International Conference on Combinatorial synthesis of natural products, December 1997).

The most recent approach which is frequently used for the syntheses of PGs involves the conjugate addition of an organometallics to an α-substituted 4-hydroxy 2-cyclopentenone (M.P.L. Caton in "New *Synthetic Routes to Prostaglandins*"., Academic Press **N.Y.,** pg 105, 1982 and F. Sato *et al.,, J. Org Chem.*, **59,** 6153, 1994). The two-component process consists of two independent but complementary routes: introduction of a o-side chain to an *endo*-enone bearing an α-side chain and introduction of α-chain to an *exo*-enone bearing an o-side chain.

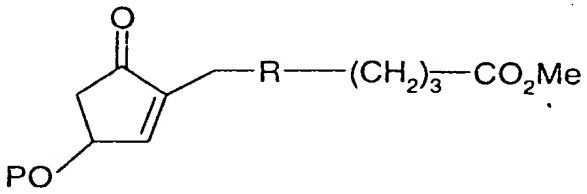
The present invention involves the use of enantiomerically pure *endo*-enone (II) bearing an α-sidechain and the desired o-chain was introduced via conjugate addition of a higher order cuprate generated using an enantriomerically pure β-chain iodide (VI). The delineated process describes the synthesis of *endo*-enone (II) in an excellent optical purity (> 99% ee), following the alkylation chemistry of the stabilised carbanion and its resolution using the technique of ultrasound mediated enzymatic irreversible transesterification. Herein, we have described a process for the preparation of enantiomerically pure β-chain alcohol (> 99% ee) and its conversion to component B of very high optical purity. The reported procedures for the two component coupling process involve the conjugate addition of a higher order cuprate to the optically pure enone and are often encountered with an incomplete addition. This involves the recovery of the unreacted starting enone by exhaustive column chromatographic separation. In the present process we have demonstrated the use of Lewis acids such as BF_3-etherate to activate the enone at temperature such as -78°C, followed by the conjugate addition of the higher order cuprate, resulting in the complete consumption of the enone. This procedure circumvents the chromatographic purification of the coupled product and avoids the loss during chromatographic purification. Further post-coupling operations and the purification of the product in the last step affords carboprost methyl ester of USP specifications.

In a first aspect the invention therefore provides a process for the preparation of a compound of formula (I):



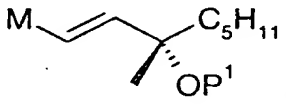
(I)

in which R is CH=CH or CH_2CH_2, and R^1 and R^2 are both hydrogen or together form a bond, which comprises coupling a compound of formula (II);



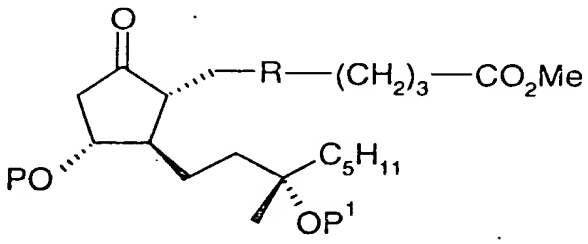
(II)

in which R is as defined in formula (I) and P is a protecting group, with a compound of formula (III):



(III)

in which P^1 is a protecting group and M is a cuprate to give a compound of formula (IA):



(IA)

in which P and P^1 are as defined above, and there after in any order:

- optionally reducing the compound (IA)
- removing any protecting groups.

Suitably R is CH=CH or CH_2CH_2, preferably R is CH=CH.

Suitably R^1 and R^2 are both hydrogen or together form a bond such that the groups OR^1 and R^2 form a carbonyl group. Preferably R^1 and R^2 are both hydrogen.

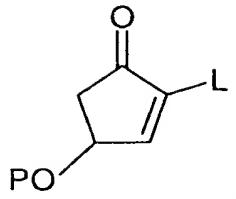
The groups P and P^1, which can be the same or different, can be any suitable oxygen protecting groups, for example tetrahydropyran and, in particular, silyl protecting groups such as t-butyldiphenylsilyl, dimethylphenylsilyl, triethylsilyl, t-butyldimethylsilyl (TBDMS), trimethylsilyl (TMS) and triisopropylsilyl . Preferably P is TBDMS and P^1 is TMS.

The reaction of compounds of formula (II) and (III) is carried out in a suitable solvent such as THF-hexane, THF-ether, preferably THF/ether. Preferably the reaction is carried out at reduced temperature, for example at about -78°C. Preferably the reaction is carried out in the presence of a Lewis acid, particularly in the presence of $BF_3.OEt_2$. It has been found that the use of $BF_3.OEt_2$ not only activates the enone at low temperatures and drives the reaction to completion, but also circumvents the problem of dehydration at the C-15 position. The higher order cuprate of formula (III) is preferably generated using an organo-lithium reagent, preferably butyl lithium.

Reduction of a compound of formula (IA) can be carried out using known reducing agents. For example reduction of the cyclopentanone is preferably carried out using a selective reducing agent such as K-selectride to give the desired cyclopentanol isomer. Reduction of the triple bond can be carried out using conventional techniques such as Lindlar hydrogenation.

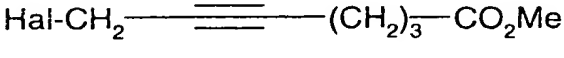
Removal of protecting groups can be carried out using conventional procedures. For example when protecting groups P and P^1 are both silyl groups deprotection of both groups can be achieved using a fluoride reagent such as TBAF in a suitable solvent such as THF. Preferably the cyclopentanone moiety is reduced, followed by deprotection of the groups P and P^1 followed by reduction of the triple bond to furnish the desired compounds of formula (I).

Compounds of formula (II) can be prepared from compounds of formula (IV):



(IV)

in which P is as defined in formula (II) and L is a leaving group with a compound of formula (V):



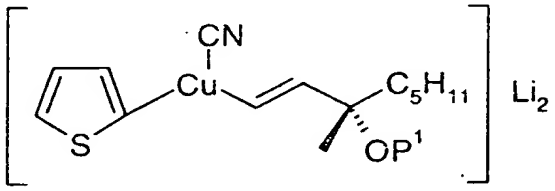
(V)

in which Hal is halogen in the presence of an organolithium reagent. Preferably L is a group such as a -SePh to stabilise the carbanion generated and Hal is bromo or iodo, preferably iodo.

Compounds of formula (IV) in which L is SePh can be prepared from the corresponding enone and phenylselenyl chloride using literature procedures. The enone can be prepared by protecting the corresponding alcohol, for example by treating with TBDMS chloride conventional conditions.

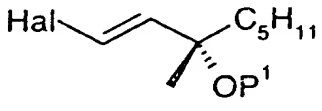
Compounds of formula (V) can be prepared by halogenation of the corresponding alcohol which in turn is prepared using known procedures as exemplified herein.

The compound of formula (III) is a suitable cuprate, in particular a higher order cuprate and preferably a thienyl cuprate, in particular dilithium [3-methyl, 3-(trimethylsilyl)oxy octyl}-2-thienyl cyanocuprate of formula (IIIA):.



(IIIA)

which is prepared from the corresponding halide of formula (VI):



(VI)

in which Hal is halogen, in particular iodo, and P^1 is a protecting group as defined in formula (III), preferably a TMS group. This compound can be prepared according to the procedures exemplified herein.

Novel intermediates form a further aspect of the invention.

The invention is illustrated by the following Examples.

Intermediate 1
SYNTHESIS OF METHYL 7-IODO HEPTA-5-YONATE

a) Methyl-7-hydroxy hept-5-ynoate.

The title compound was prepared according to the method of R.J.K. Taylor *et al.*, Tetrahedron, **42**, 5849-56 (**1986**) as an oil, bp 130 - 132°C at 0.5mm Hg.
^{1}H NMR ($CDCl_3$): δ 4.15 (m, 2H), 3.6 (s, 3H), 3.0 (bs, 1H, exchanges with D_2O), 2.35 (t, 2H), 2.25 (t, 2H) and 1.75 (q, 2H).

b) Methyl-7-iodo hepta-5-yonate:

The title compound was prepared from the above α-alcohol according to the method of Carl Johnson *et al.*, JACS, **110**, 4726-35 (**1988**) as an oil, bp 110 - 113°C at 0.9 mm Hg.

^{1}H NMR ($CDCl_3$): δ 3.6 - 3.7 (bs,5H), 2.4 (t, 2H), 2.25 (t, 2H), 1.75 (q, 2H).

Intermediate 2.
SYNTHESIS OF RACEMIC 4-HYDROXY CYCLOPENTENONE.

The title compound was prepared according to the method of M. Minai, Jap. Patent., Kokai No. 62236, **1982.**

^{1}H NMR ($CDCl_3$): δ 7.55 (dd, J = 6Hz, 1.5Hz, 1H), 6.2 (d, J = 6 Hz, 1H), 5.05 (m, 1H), 2.75 (dd, J = 17 Hz, 6 Hz, 1H), 2.25 (dd, J = 17 Hz, 6 Hz, 1H) and 2.0 (bs, 1H, exchanges with D_2O).

Intermediate 3
Synthesis of 1-Iodo(*S*)-methyl-3-(trimethylsilyloxy)-oct-2-ene.

a) Racemic 3-methyl-octa-1-yn-3-ol

A 3-necked 3litre r.b. flask was cooled under a stream of nitrogen gas and was fitted with mechanical stirrer through the centre neck. Side arm was connected to a socket with gas inlet and a cold, finger condenser. Another side arm was connected to a nitrogen inlet under static pressure. The cold finger condenser was charged with dry ice-acetone mixture

(-78°C) and the reaction flask was kept in an insulated bath. Anhydrous ammonia gas (dried through a wash bottle containing KOH pellets) was bubbled at a steady rate through the gas inlet in an atmosphere of nitrogen, whereupon ammonia condenses into the reaction flask. It took around 2 hr. to condense ammonia gas to obtain around 1.6 Litre of liquid ammonia. At this stage the condensation of ammonia was stopped and in the place of ammonia bubbler was connected the nitrogen inlet. The other side arm was stoppered. Sodium metal was cut into small pieces and washed with anhydrous hexane. After the addition of the first piece while stirring mechanically, the colour of the reaction mixture turned blue as the metal dissolved. As soon as the blue colour persists, ferric nitrate was added through the side arm, whereupon the reaction becomes exothermic and upon stirring the blue colour discharges to afford the greyish white sodium amide. The addition of sodium metal was continued. Upon addition of sodium metal, the appearance of blue colour was observed and as the stirring is continued, the greyish white coloration is observed. After the complete addition of the metal (it took 1 hr. for the completion of addition of sodium metal), the reaction mixture was stirred for about 0.5 hr to ensure the complete formation of sodium amide. During the whole process a static pressure of nitrogen gas and the temp. of -78°C in the cold finger condenser was maintained. Through one side arm, a gas inlet tube was inserted and bubbling of acetylene gas was continued at a steady rate (acetylene was bubbled through a paraffin trap and an empty trap kept at -78°C) over a period of 5 hr. to ensure the complete formation of sodium acetylide. Acetylene bubbling was stopped and a pressure equalising dropping funnel was fitted to one side arm of the reaction flask and was charged with 2-heptanone (287g, 2.511 mol) in anhydrous ether (75 ml). The contents were then added dropwise while stirring over a period of 1 hr. (exothermic reaction!). The dropping funnel was rinsed with ether (40 ml) and the washings were added to the reaction flask. The contents in the reaction flask were stirred vigorously and the bubbling of acetylene gas was continued for another 3 hr. and allowed to stand overnight without stirring. The temp. in the cold finger condenser was raised to ambient temp. slowly the facile evaporation of ammonia gas.

Workup: The mechanical stirrer and the cold finger condenser was dismantled and the 3-necked flask was cooled to 0°C under nitrogen using an ice-bath and to this was added NH_4Cl solution in water in small lots of 50 ml each. The reaction mixture was stirred at 0°C for a further 0.5 hr. and warmed to RT and stirred at RT for 2 hr. The resultant solution was filtered over a celite bed using a G-3 sintered funnel. The residue was washed with pet ether (2 x 150 ml). The contents were transferred to a separatory funnel and the aqueous layer was separated. Aqueous layer was extracted with pet ether (3 x 500 ml).

Combined PE portion was washed with water (2 x 500 ml), brine (100 ml) and dried over anhydrous Na_2SO_4. Removal of volatiles *in vacuo* afforded 352 gm of crude β-chain alcohol. This was further purified by distillation in vacuum (bp 76-78°C at 17mm of Hg) to get 330 gm of β-chain alcohol (2.360 Mols, 94% yield). Initial forerun in the distillation furnished unreacted 2-heptanone (bp. 67-69°C at 17mm of Hg). This was recycled with next batch for the preparation of racemic octynol.

Yield of racemic β-chain alcohol: 330 gm, 2.360 mols, 94%. Purity of > 99% was ascertained by GC analysis: column: OV-101, 90°C, RT for octynol: 5 min: for heptanone: 2.5 min.).

b). 3-Methyl-3-carboxy-oct-1-yn-3-ol hydrogen phthalate.

i). Recrystallisation of phthalic anhydride - representation procedure.

A precooled 5 litre r.b. flask with a magnetic stirring bar was charged with 570 gm of phthalic anhydride and 2.3 litre of chloroform. The contents were refluxed on a water bath for 0.5 hr and filtered hot on a sintered funnel. Undissolved residue is phthalic acid. The filterate was left in the refrigerator in a tightly stoppered flask to get the crystalline phthalic anhydride. This was filtered, washed with hexane and dried in a desiccator. mp 130-131°C.

ii) 3-Methyl-3-carboxy-oct-1-yn-3-ol hydrogen phthalate.

A pre-cooled 5 litre r.b. flask with a magnetic stirring bar was charged with the racemic octynol (0.92kg, 6.57 mol), phthalic anhydride (0,979kg, 6.606 mol), DMAP (0.08kg, 0.658mol) and triethylamine (0.67kg, 6.617mol). The reaction mixture was refluxed at 80°C for 6 hr and allowed to cool to RT and stirred overnight. The progress of the reaction was monitored by TLC (solvent system: 20% EtOAc in PE) for the disappearance of the starting octynol. The reaction mixture was left overnight at RT.

Workup: A 20 Litre r.b. flask with a flange and a mechanical stirring assembly was charged with 7.4 Litre of water and 0.731 litre of conc. HCl and cooled to 0°C using an ice bath. To this mixture was added the hemiphthalate reaction mixture while stirring, followed by the addition of chloroform (2.3 litre). The stirring was continued for 1 hr. The organic layer was separated and the aqueous layer was extracted with chloroform (3 x 3

litre). Combined organic layer was washed with water (2 x 500 ml) and brine (500 ml). This was dried over anhydrous Na_2SO_4 and volatiles were removed using a rotary evaporator and dried in high vacuum.

In another 20 Litre r.b. flask with a flange and a mechanical stirring assembly was taken petr. ether 5.5 Litre) and cooled to 0°C. Hemiphthalate from the earlier step was poured into PE while stirring and stirred for 1 hr., whereupon the desired hemipthalate ester crystallises. This was filtered using a buchner funnel, residue washed with cold PE (500 ml) and dried in suction. This residue was air dried (m p 61-62°C, 0.915 Kg,). The mother liquor from filitration was concentrated *in vacuo* using a rotary evaporator and kept in the refrigerator to get an additional lot of hemiphthalate ester (2^{nd} crop, 0.43 Kg, m p 61-62°C). However, by repeating the sequence for the third crop, the compound obtained (0.151 Kg) showed higher m p and hence was kept aside and taken up for the recovery of racemic octynol.

Yield of hemiphthalate ester: 1.348 Kg, 71%.

c). Brucine phthalate of 3-Methyl-oct-1-yn-3-ol.

A pre-cooled 20 litre flanged r.b. flask with a mechanical stirring assembly was charged with the hemiphthalate ester of racemic octanol (0.94kg, 3.262 mol), brucine (1.432kg, 3.327 mol) and anhydrous acetone (3.75 l). The reaction mixture was heated at 50°C for 1 hr and allowed to cool to RT and stirred overnight at RT.

Workup: The precipitated solid was filtered using a buchner funnel and washed with cold acetone (2 x 250 ml) to get rid of the contamination of undesired diastereomer. The resulting solid was air dried.

Yield: 0.739 Kg, 1.028 mols, 31.5%. m p 158-159°C, $[\alpha]_D$ = - 12.0° ± 0.5(c 0.88, EtOH). The mother liquor was kept aside for the recovery of brucine.

d). Hemiphthalate ester of (*S*)-octynol from brucine salt: (*S*)- 3-Methyl-3-carboxy-oct-1-yn-3-ol hydrogen phthalate.

A pre-cooled 20 litre flanged r.b. flask with a mechanical stirring assembly was charged with brucine salt (0.827kg, 1.15 mol) and ether (8.2 l). To this was added conc. HCl (0.83 l) in small lots at 0°C while stirring. The reaction mixture was stirred at 0°C for 2 hr and allowed to warm to RT.

Workup: The contents were transferred to a separatory funnel and the ether layer was separated. Aqueous layer was extracted with ether (2 x 500 ml). Combined ether layer was washed with water (2 x 250 ml), brine (250 ml) and dried over anhydrous Na_2SO_4. Removal of volatiles *in vacuo* afforded the desired hemipthalate ester of (*S*)-octynol as a viscous material. The aqueous layer was discarded.
Yield of hemiphthalate ester of (*S*)-octynol: 0.332 Kg (near quantitative). This was used as such without purification for further reaction.

e). (*S*)-3-Methyl-oct-1-yn-3-ol.

A pre-cooled 20 litre flanged r.b. flask with a mechanical stirring assembly and a reflux condenser was charged with the hemiphthalate ester of (*S*)-octynol (0.332 kg, 1.151 mol) and to this was added NaOH solution (0.504 kg in 3.6 l water) at RT. The reaction mixture was refluxed on a water bath for 2 hr. The reaction mixture was cooled to RT, whereupon the octynol layer separates. The contents were transferred to a separatory funnel and the supernatent layer was separated. The aqueous layer was extracted with petroleum ether (3 x 500 ml) and mixed with the octynol fraction. Combined organic portion was washed with distilled water (3 x 500 ml) till the pH is 7. The organic portion was dried over anhydrous Na_2SO_4 and removal of volatiles furnished 155 gm (96%) of crude (*S*)-octynol which was further purified by distillation *in vacuo*. b p. 73-76°C at 14-15 mm of Hg.
Yield: 128.87 gm, 0.921 mols, 80%, $[\alpha]_D$ = -2.3° ± 0.5(c 2.7, EtOH). Reported $[\alpha]_D$ = -2.33° (c 2..625, EtOH).

f). (*S*)-3-Methyl-3-(trimethylsilyl)oxy-oct-1-yne.

A pre-cooled 1 litre r.b. flask with a magnetic stirring bar was charged with (*S*)-octynol (29g, 0.207 mol) and DMF. The reaction mixture was cooled to 0°C (ice-bath) under nitrogen atmosphere. To the reaction mixture was added imidazole (39.44g, 0.58 mol) in small portions (of ~ 5 gm) at 0°C and stirred to 15 min. To the reaction mixture was added TMS chloride (33.72g, 0.310 mol) dropwise by means of a syringe over a period of 45 minutes and then stirred at 0°C for 1hr. The reaction mixture was allowed to warm to RT and stirred at RT overnight. The progress of the reaction was monitored by TLC (solvent system: 10% EtOAc in petroleum ether) for the disappearance of the starting alcohol.

Workup: The reaction mixture was poured into ice water (750 ml) and extracted with ether. The supernatent ether layer was separated and the aqueous layer was extracted with ether (3 x 250 ml). Combined organic portion was washed with water (2 x 100ml) and brine (50 ml). This was dried over anhydrous Na_2SO_4 and volatiles were removed using a rotary evaporatorand dried in high vacuum. This was purified by distillation under reduced pressure to get the title product:
bp. 87-90°C at 12-15 mm of Hg.
Yield: 35.09 gm, 165.5 mmols, 80%.

g). (*S*)-3-Methyl-3-(trimethylsilyl)oxy-1-(*n*-tributylstannyl)-oct-1-ene (*E*).

A pre-cooled 500 ml r.b. flask with a magnetic stirring bar was charged with TMS ether of (*S*)-octynol 7.50g, 35.37 mmol), TBTH (16.31g, 35.4 mmol) and AIBN (0.4g, 2.47 mmol). The reaction mixture was evacuated and flushed with nitrogen gas. The flask was then immersed in a preheated oil-bath at 130°C, whereupon a vigorous initiation reaction took place with the evolution of hydrogen gas. (a suitable vent is desirable). The reaction mixture was heated in an oil bath at 150°C for 3 hr and cooled to RT under nitrogen atmosphere. To the reaction mixture was added petr. ether (150 ml) and allowed to stir at RT for 15 min. The reaction mixture was filtered over a celite bed using a G-3 sintered funnel. The residue was washed with anhydrous PE (60 ml) and the combined PE layer, upon removal of volatiles afforded desired stannane derivative in quantitative yield.

Note: This derivative was stored in a tightly stoppered flask covered with an aluminium foil, under nitrogen. This is highly moisture and light sensitive! Large scale preparation would involve mixing of reactants followed by the addition of AIBN, once the operation temperature is attained.

h) 1-Iodo (*S*)-3-methyl-3-(trimethylsilyoxy)-oct-2-ene.

A pre-cooled 500 ml r.b. flask with a magnetic stirring bar was charged with stannane derivative (61.06g, 0.121 mol) and to this was added freshly distilled THF (170 ml). The reaction mixture was cooled to -78°C using dry ice-acetone bath and to this was added a solution of N-iodo succinimide (27.31g, 0.121 mol) in THF (100 ml) by means of a cannula at -78°C under nitrogen over a period of 45 min. The reaction mixture was stirred at -78°C for 1 hr. The temp. of the bath was gradually raised to RT and stirred at RT for 15 min. The progress of the reaction was monitored by TLC (solvent system: Petr. ether) for the disappearance of starting material.

Workup: The reaction mixture was poured over ice and filtered over celite bed using a G-3 sintered funnel. The filitreate was extracted with PE (4 x 100 ml). Combined PE layer was washed with water (100 ml), 10% sodium thiosulphate solution (150 ml) and finally with water (50 ml). PE portion was dried over anhydrous Na_2SO_4 and removal of volatiles *in vacuo* afforded desired iodide (0.072 Kg). This was purified by high vacuum distillation (bp.79-82°C at 0.1 mm of Hg, 0.040 Kg, 0.118 Mols, 97%.
$[\alpha]_D$ = -24.0° ± 0.5(c, 1.61: $CHCl_3$): reported $[\alpha]_D$ = -22.5° (c, 1.2: $CHCl_3$).

Intermediate 4

Preparation of 4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-one.

Prepared according to the method of R. Noyori., *et al.*, **Tetr. Lett., 28,** 4719-20 **(1987)** from 4-hydroxycyclopentanone (intermediate 2, 10.1g, 0.103 mmol), 4-DMAP (1.21g, 0.00993 mol) and triethylamine (11.46g, 0.113 mmol).

Yield: 24.03 gm (pale brownish in colour). The material had some colouring impurities which were removed via distillation under reduced pressure. (bp. 82-86°C at 1mm of Hg). Yield of the desired product: 20.02 gm, 0.158 mols, 91.7%.
^1H NMR ($CDCl_3$): δ 7.4 (m, d, 1H), 6.1 (d, 1H), 4.9 (m, 1H) 2.6 (dd, 1H), 2.15 (d, 1H), 0.8 (s, 9H), 0.1 (s, 6H). The purity of the material was established by HPLC using a chiracel-OD column using 1.5% isopropan-2-0l in *n*-haxane.

Intermediate 5

a) Preparation of racemic 4-[(*t*-butyldimethylsilyl)oxy]-2-(phenylseleno)-2-cyclopenten-1-one

Prepared according to the method of T. Toru, *et al.*, **J.Org. Chem., 57,** 4719-20 **(1992)** from TBS-derivative 4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-one.

(23.84g, 0.112 mol), phenyl selenyl chloride (32.32g, 0.169 mol) and pyridine (14.69g, 0.186 mol).

Yield 37.14g, 90%.
^1H NMR ($CDCl_3$): δ 7.3-7.7 (m, 5H), 4.85 (m, 1H), 2.8-2.9 (dd, 1H) 2.35 (d, 1H), 0.8 (s, 9H) and 0 (s, 6H).

b). Preparation of Methyl 7-(3-Hydroxy-5-oxo-1-cyclopentene-1-yl)-5-heptynoate via a two-component coupling process.

Prepared according to the method of T. Toru, *et al.*, **J.Org. Chem., 57,** 3145-3152 **(1992)** from selenyl derivative 4-[(*tert*-butyldimethylsilyl)oxy]-2-(phenylseleno)-2-cyclopenten-1-one.

(16.65g, 45.3 mmol), bis(tributylstannane (28.94g, 49.91 mmol), n-BuLi (35.6 ml of 1.4M in hexane, 49.91 mmol), iodine (25.35g, 95.28 mmol) and HMPA (26ml) in THF.

The product was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether. Yield of the pure product: 11.11 gm, 31.76 mmols, 70%.

^{1}H NMR ($CDCl_3$): δ 7.3 (s, 1H), 4.9 (m, 1H), 3.65 (s, 3H), 3.0 (bm, 3H), 2.75 (dd, 1H) 2.45 (t, 2H), 2.25 (bt, 2H), 1.8 (q, 2H), 0.8 (s, 9H) and 0.1 (s.6H).

c). Methyl 7-(3-Hydroxy-5-oxo-1-cyclopentene-1-yl)-5-heptynoate

Prepared according to the method of E.J. Corey *et al*, **JACS., 94,** 6190-91 **(1972)** from the TBS derivative (6.02g, 17.22 mmol) , Methyl-7-[-3-*tert*-butyldimethylsilyl)oxy]-5-oxo-1-cyclopenten-1-yl]-hept-5-ynoate in a solution of AcOH: THF: water (3:1:1).

Yield 2.44 gm, 10.33 mmols, 60%. TLC: solvent system: 70% EtOAc in petroleum ether. ^{1}H NMR ($CDCl_3$): δ 7.4 (bs, 1H), 5.0 (bs, 1H), 3.65 (s, 3H), 3.0 (bm, 3H), 2.85 (dd, 1H) 2.45 (m, 2H), 2.25 (m, 2H), and 1.8 (q, 2H).

d) ENZYMATIC IRREVERSIBLE TRANSESTERIFICATION USING Lipase IN VINYL ACETATE IN A SONICATOR BATH:

Prepared according to the methods of K.A. Babiak, *et al.*; **J. Org.Chem., 55**, 3377-81, **(1990)** and G Lin, *et al.*, **Tetr.Lett., 36**, 6067-68 **(1995)** from the hydroxy-enone (4.7g, 19.91 mmol, Methyl-7-[(3-hydroxy)-5-oxo-1-cyclopentene-1-yl]-hept-5-ynote and PPLipase and/or HPLipase (crude, 7.5g) in vinyl acetate with sonication.

Yield of desired acetate 2.40g, 43%.

^1H NMR ($CDCl_3$): δ 7.4 (bs, 1H), 5.75 (m, 1H), 3.65 (s, 3H), 3.05 (bm, 3H), 2.85 (dd, 1H), 2.4 (t, 2H), 2.25 (m, 2H), 2.1 (s, 1H) and 1.8 (q, 2H).

e) DEACETYLATION USING GUANIDINE IN METHANOL

Preparation of a stock solution of Guanidine in Methanol:

Prepared according to the method of K.A. Babiak, *et al.*, **J. Org.Chem., 55**, 3377-81, **(1990)** from guanidine carbonate (28.4g, 0.158 mol), sodium metal (3.56g, 0.155 mol) in methanol (0.308 l).

Methyl-7-[((*R*)-3-hydroxy)-5-oxo- 1 - cyclopentene-1 -yl]-hept-5-ynote.

Prepared according to the method of : K.A. Babiak, *et al.*, **J. Org.Chem., 55**, 3377-81, **(1990)** from the (R) acetate (1.905g, 6.85 mmol)and guanidine in methanol.

Note: it is recommended to carry out the deacetylation on a small scale before performing deacetylation on a rather big scale because of the sensitive nature of β-hydroxy ketone.

Yield: 1.130 gm, 4.788 mmols, 70% yield, (90 optically pure). This was used for further upgradation of optical purity using PPLipase and/or HPLipase as described below.

Procedure: Same as the earlier enzymatic resolution using a sonicator bath. Enrichment was complete in 5 days. Desired product was isolated by flash chromatography in 40-50% EtOAc in PE eluate. Yield of (*R*)-Acetate: optical purity: > 99.9%. This was further deacetylated using guanidine in methanol to get 1.553 gm of optically pure alcohol (5.586 mmols, > 99.9% optically pure by chiral HPLC analysis.

f) MITSUNOBU INVERSION TO CONVERT UNDESIRED ENANTIOMER TO THE DESIRED ENATIOMER:

Prepared according to the methods of K.A. Babiak, *et al.*, **J. Org.Chem., 55**, 3377-81, **(1990).**

A precooled 250 ml. r.b flask with a septum inlet and a magnetic stirring bar was charged with (S)-alcohol (2.58g, 10.93 mmol of 88% optical purity), Ph_3P (5.74g, 21.86 mmol) and freshly distilled THF. The reaction mixture was cooled to 10°C and to this was added formic acid by means of a syringe, followed by the addition of diisopropylazodicarboxylate

(DIAD, 4.42g, 21.86 mmol) and slowly warmed to RT. The pale yellow reaction mixture was stirred at RT for 12 hr. in an atmosphere of nitrogen gas. The progress of the reaction was monitored by TLC (solvent system: 70% EtOAc in PE).

Workup: The solvent was removed *in vacuo* under pressure using a rotary evaporatorand the resulting brownish residue was dissolved in ether (70 ml) and triturated with *n*-hexane (165 ml) to precipitate phosphorous salts. The mixture was stirred at RT for 30 min. and filtered over a G-3 sintered funnel, washed with ether (2 x 50 ml). Combined organic portion was transferred to another r.b. flask and volatiles were removed *in vacuo* using a rotavapor. The resulting residue was dissolved in MeOH (120 ml) and to this was added alumina (activated, neutral, 100 gm) and stirred at RT overnight. The progress of the reaction was monitored by TLC (solvent system: 70% EtOAc in PE). The reaction mixture was filtered on a G-3 sintered funnel and the residual alumina was repeatedly washed with MeOH (3 x 100 ml), combined filterate was subjected to flash evaporation using a rotary evaporator to give 13.805 gm of the crude product. This was further purified by flash chromatography over a column of silicagel (400 gm, 200-400 mesh). Initial elution with a gradient of 15-60% EtOAc in petroleum ether gave undesired 1,2-diisopropyl dicarboxyhydrazine and the desired alcohol was obtained in 80-95% EtOAc in PE. The HPLC analysis using Chiracel-OD column indicated clean inversion at the chiral centre (no noticeable racemisation) with an optical purity of 88% of the (***R***) isomer.

This product was further subjected to enzymatic transesterfication using HPL in a sonicator to furnish desired (***R***)-acetate of >99% optical purity. Yield: 1.891 gm, 6.802 mmols, 70%. This was further deacetylated using guanidine in methanol, to get the desired (***R***)-alcohol in > 99% optical purity. Yield: 1.166 gm, 4.94 mmols, 73% yield.

g). Methyl-7-[(*R*)-3-*tert*-butyldimethylsilyl)oxy]-5-oxo-1-cyclopenten-1-yl]-hept-5-ynoate.

To a precooled 250 ml r.b. flask with a septum inlet and a magnetic stirring bar was taken TBDMS chloride (1.90g, 12.64 mmol) and dichloromethane. The solution was cooled to 0°C using an ice-bath and to this was added imidazole (1.60g, 23.66 mmol) in one portion, followed by the addition of DMF. The reaction mixture was stirred at 0°C for 15 min. In another pre-cooled flask was taken (*R*)-enone alcohol (1.99g, 8.4 mmol) in anhydrous CH_2Cl_2 (3 ml) and this was transferred to the reaction flask under nitrogen by means of a cannula. The washings (1 ml) were transferred to the reaction flask and stirred at 0°C for 2

hr. The reaction mixture was allowed to warm to RT and stirred further overnight (~ 10 hr.). The progress of the reaction was monitored by TLC (solvent system: petroleum.ether:EtOAc, 3:7).

Workup: The reaction mixture was poured over ice-water and extracted with dichloromethane (3 x 100 ml). Combined organic layer was washed with water (30 ml) and with brine. Organic portion was dried over anhydrous Na_2SO_4, removal of volatiles *in vacuo* furnished 3.80 gm of oily material, which was further purified by flash chromatography on a column of silicagel (150 gm, 200-400 mesh) in 15-25% EtOAc in pet. ether eluate. Yield of the desired product: 2.90 gm, 4.66 mmols, 70%. TLC: solvent system: 70% EtOAc in petr. ether.

^1H NMR ($CDCl_3$): δ 7.4 (bs, 1H), 5.0 (bs, 1H), 3.65 (s, 3H), 3.0 (bm, 3H), 2.85 (dd, 1H), 2.45 (m, 2H), 2.25 (m, 2H) and 1.8 (q, 2H). The purity of the material was established by HPLC using a chiracel-OD column using 7% isopropan-2-ol in *n*-hexane.

Example 1.

a). 2-Thienyllithium:

Procedure: In a pre-cooled 100 ml r.b. flask with a septum inlet and a magnet stirring bar was taken freshly distilled THF (30 ml) and thiophene (1.59 ml, 20 mmols). The reaction mixture was cooled to -60°C (dry ice-$CHCl_3$ bath) and to this was added *n*-BuLi (16.7 ml, 1.2M in hexane) dropwise by means of a syringe over a period of 15 min. The reaction mixture was stirred at -60°C for 1 hr. to ensure the completion of metallation. The colour of thienyllithium in THF was pale yellow.

b) Preparation of vinyllithium:

Procedure: A pre-cooled 100 ml r.b. flask with a septum inlet and a magnetic stirring bar was charged with B-chain iodide TMS ether (6.8g, 20 mmol) in 30 ml of THF (freshly distilled, anhydrous) and the contents cooled to -78°C (dry ice-acetone bath) under nitrogen. To this was added *n*-BuLi (21 mmol, 17.5 ml) dropwise by means of a syringe at -78°C over a period of 30 min. The reaction mixture became turbid with pale yellow precipitate of vinyllithium indicating the completion of reaction. The contents were further stirred at -78°C or 1 hr.

c) TWO-COMPONENT COUPLING PROCESS:

Procedure: To a precooled 500 ml r.b. flask with a septum inlet was added Cu(I)CN (20 mmol, 1.79gm) and a magnetic stirring bar. The flask was capped with a rubber septum and heated with a heat gun under high vacuum to remove any traces of moisture, allowed to cool and purged with nitrogen. THF (30 ml) was added and the suspension cooled to -22°C (dry ice-CCl_4 bath) under nitrogen. To this was added the solution of preformed 2-thienyllithium (step **a**) dropwise by means of a cannula over a period of 10 min. The contents were washed with THF (5 ml) and added to the flask, whereupon the solution became homogenous (pale yellow colour) to afford the desired lower order cuprate. The reaction mixture was further stirred at -22°C for 1 hr.

To the above solution of the lower order cuprate was added the solution of vinyl lithium (step **b**) dropwise by means of a cannula over a period of 10 min at -22°C, washed with THF (5 ml) and the solution stirred at -22°C for a further 1 hr. to provide a homogenous higher order cuprate (clear solution, pale yellowish orange colour). The resulting cuprate solution was cooled to -78°C (dry ice-acetone bath).

In a precooled 100 ml pear shaped flask was taken (*R*)-enone TBDMS ether (> 99% optically pure, 3.5 gm, 10 mmols) and to this was added anhydrous ether (40 ml) by means of a syringe. The contents were cooled to -78°C using a dry ice-acetone bath for 10 min. To this was added BF_3:OEt_2 (1.29 ml, 10.5 mmols) dropwise while stirring, by means of a syringe at -78°C and left at this temp. for 5 min. This solution was then added dropwise (very slow dropwise addition!) to the solution of the higher order cuprate (obtained in step-**c**) at -78°C under nitrogen by means of a cannula over a period of 45 min. The flask of enone was washed with ether (5ml) and the washings transferred to the reaction flask over a period of 45 min. The stirring was continued at -78°C for 1.5 hr (progress of the reaction monitored by TLC, solvent system: pet. ether -10% EtOAc, for the disappearance of the starting enone). The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 ml) at -78°C and warmed to RT. The reaction mixture was poured into a mixture of 150 ml distilled water and 300 ml of ether. The aqueous layer was extracted with ether (3 x 100 ml) and the combined organic portion was washed with brine, dried over anhydrous Na_2SO_4. Removal of volatilities *in vacuo* afforded an oil (11.35 gm). This product was used as such for the further sequence without chromatographic purification. TLC: solvent system: pet ether-10% EtOAc: A part of the sample was

purified by flash chromatography (silicagel, 1:20 ratio, 200-400 mesh) and the desired product was obtained in 20% EtOAc in PE eluate for characterisation, R_f 0.31, solvent system: pet.ether-10% EtOAc:
^1H NMR ($CDCl_3$): δ 0.05 (s, 6H); 0.8-0.9 (m, 12H); 1.1-1.6 (m, 10H); 1.7-1.8 (m, 3H); 2.0-2.3 (m, 6H); 2.4 (t, 2H, J = 7.4 Hz); 2.6-2.9 (m, 3H); 3.65 (s, 3H); 4.1 (m, 1H); 5.3-5.5 (m,2H).

Example 2.
(5,6-Didehydro-11-O-(*tert*-butyldimethylsilyl)-15-O-(trimethylsilyl-13-(*S*)-methyl - PGE_2 methyl ester

Procedure: To a flame dried 250 ml r.b. flask with a septum inlet and a magnetic stirring bar, was added the crude TCC product [5,6-Didehydro-11-O-*tert*-butyldimethylsilyl)-15-O-(trimethylsilyl)-13-(*S*)-methyl - PGE_2 methyl ester]. (11.35 gm, from 10 mmol of the enone) in THF (anhydrous, 35 ml). The solution was cooled to -78°C and treated with a solution of K-selectride (32.85 ml, 30 mmol, 0.9M solution in THF) dropwise by means of a syringe. The reaction mixture was allowed to stir at -78°C for 1.5 hr. and to this was added dropwise a 30% aqueous solution of H_2O_2 (4.54 ml, 40 mmol). Stirring was continued for another 15 min, the cooling bath was removed and the reaction mixture warmed to room temperature. Water (20 ml) was added and the organic phase separated. The aqueous phase was extracted with EtOAc (3 x 50 ml). The combined organic layer was washed with brine (2 x 20 ml) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacue* furnished 13.516 gm of the desired crude product. This was used as such for further desilylation. TLC solvent system: 20% EtOAc in PE, R_f 0.2.

A small portion of the selectride reduction product obtained in the earlier step was purified by flash chromatography using silicagel (60 gm, 200-400 mesh). The desired product was obtained in pet ether-30% EtOAc eluate: R_f 0.2 (solvent system pet.ether-20% EtOAc). ^1H NMR ($CDCl_3$): δ 0.05 (s,6H); 0.8-0.9 (m, 12H); 1.2-1.6 (m, 10H); 1.7-1.9 (m, 3H); 2.1-2.3 (m, 10H); 2.4 (t, 2H J = 7.4 Hz); 3.65 (s, 3H); 3.9-4.0 (bs, 1H); 4.2-4.3 (bs, 1H); 5.3-5.5 (m, 2H).

Procedure: To a precooled 250 ml r.b. flask with a septum inlet and a magnetic stirring bar was added the crude selectride reduced product (13.52 gm) and THF (anhydrous, 35 ml). The solution was cooled to 0°C and to this was added a solution of tetra-*n*-butyl ammonium flouride (30 mmols, 30 ml of 1M soln. In THF, 3 equiv.) dropwise by means

of a syringe over a period of 5 min. Stirring was continued for 0.5 hr. at 0°C and 5 hr. at room temperature until the completion of reaction by TLC analysis (solvent system: EtOAc). THF was removed *in vacao* and water (20ml) was added, extracted with EtOAc (3 x 30ml). The combined EtOAC layer was washed with water (2 x 10 ml), brine (2 x 10ml) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded 5.409 gm of the crude product. This was further purified by flash chromatography over a column of silica gel (350 gm, 200-400 mesh). The desired product was obtained in EtOAc eluate as a pale brown oil (1.94 gm, 5.10 mmols), 51% yield based on the starting (R) eonone: Rf 0.5 (solvent system EtOAc). This was dissolved in anhydrous ethyl acetate (50 ml) and to this was added 0.400 gm of the activated charcoal and stirred in an atmosphere of nitrogen at RT for 1 hr. This solution was filtered over celite bed using a G-4 sintered funnel, washed with EtOAc (30 ml): Removal of volatiles *in vacuo* afforded 1.95 gm of the crude product, which was purified by flash chromatography over a column of silica gel (150 gm, 200-400 mesh) and the desired product was obtained in ethyl acetate eluate as a colourless viscous oil, which solidified on storing at -22°C as a colourless solid (chloroform-methanol gradient system can also be used for the flash chromatographic purification). Yield: 1.90 gm, 5 mmols 50%. ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 6.8 Hz); 1.1-1.5 (m, 8H); 1.6-1.9 (m, 7H); 2.1-2.5 (m, 10H); 3.65 (s, 3H); 3.85-4.0 (bs, 1H); 4.3-4.4 (bs, 1H) 5.3-5.6 (m, 2H): ^{13}C NMR ($CDCl_3$): δ 173.64, 139.50, 127.92, 79.56, 79.48, 77.2, 72.28, 72.02, 54.53, 51.4, 48.84, 42.56, 42.0, 32.69, 32.0 26.51, 23.87, 23.68, 22.35, 17.98, 16,97 and 13.78.

Note For the desilylation reaction it is essential to use anhydrous TBAF in THF. Use of TBAF.3 H_2O does not give the desired product in good yield.

Preparation of carboprost methyl ester, (15*S*)-15- Methyl PGF2α methyl ester or IUPAC nomenclature as mentioned in USP as Prosta-5,13-dien-1-oic methyl ester, 9,11,15-trihydroxy-15-methyl-(5Z,9α,11α,13*E*,15*S*) or (*Z*)-7-[1*R*,2*R*,3*R*,5*S*)-3-5-Dihydroxy-2-[(E)-(3*S*)-3-hydroxy-3-methyl-1-octenyl]cyclopentyl]-5-heptenoic methyl ester.

Selective Lindlar hydrogenation was performed in batches of 0.500 gm up to 1 gm scale. The following procedure is representative.

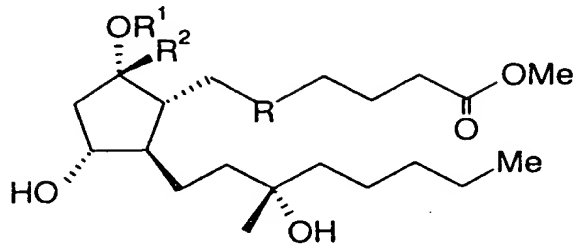
A precooled 2-necked 1000 ml r.b. flask was charged with the desilylated product (1.065 gm, 2.80 mmols) and to this was added a preformed mixture of benzene (100 ml) and

cyclohexane (300 ml) by means of a cannula under nitrogen. To the reaction mixture was added 0.315 gm of Pd over $CaCO_3$ poisoned with lead under nitrogen. The reaction mixture was evacuated in vacuo and flushed with hydrogen gas and through the reaction mixture was bubbled hydrogen gas while stirring at a rate of 45 bubbles per minute over a period of 90 min. An aliquot was taken out at regular time intervals and the progress of the reaction was monitored by ^{13}C NMR analysis (approx. 1.5 hrs, ^{13}C NMR analysis should indicate the total disappearance of alkynyl carbon at δ 80 ppm). The reaction mixture was filtered using a G-4 sintered funnel, the residue washed with EtOAc. (The catalyst recovered could be recycled). Concentration of the organic phase *in vacuo* furnished the desired carbonprost methyl ester as a viscous colourless oil (1g). This was further purified by chromatography over silica gel in EtOAc eluate (chloroform-methanol gradient system can also be used for the flash chromatographic purification). ^{1}H NMR ($CDCI_3$: δ 0.85 (t, 3H, J = 6.8 Hz); 1.1-1.5 (m, 8H); 1.6-1.9 (m, 7H); 2.1-2.5 (m, 10H); 3.65 (s, 3H); 3.85-4.0 (bs, 1H); 4.3-4.4 (bs, 1H); 5.3-5.6 (m, 4H): ^{13}C NMR ($CDCI_3$): δ 173.79, 139.0, 129.26, 129.0, 128.5, 77.9, 72.6, 72.5, 55.6, 51.4, 50.4, 42.58, 33.16, 32.03, 27.23, 26.33, 25.29, 24.55, 23.62, 22.4 and 13.82.

This product was further purified by preparative reversed phase HPLC using a preparative ODS (C-18) SHIMPAK column (20 x 250 mm) and using a mobile phase of acetonitrite-water (1:1): UV detection: 210 nm. The preative HPLC was done in batches of 0.170 gm and the recovery of the pure carbonprost methyl ester of USP specifications was ~ 65%.

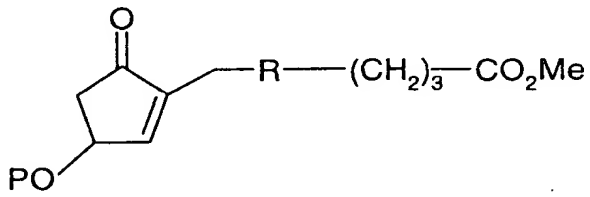
WE Claim

1. A process for the preparation of a compound of formula (I):



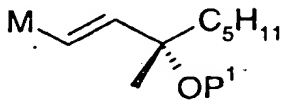
(I)

in which R is CH=CH or CH_2CH_2, and R^1 and R^2 are both hydrogen or together form a bond, which comprises coupling a compound of formula (II);



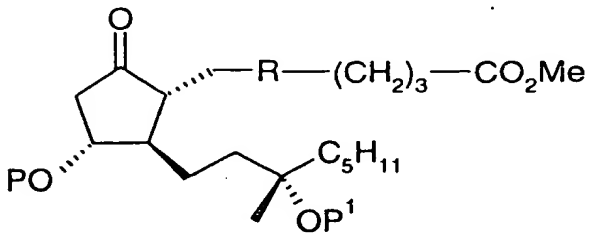
(II)

in which R is as defined in formula (I) and P is a protecting group, with a compound of formula (III):



(III)

in which P^1 is a protecting group and M is a cuprate to give a compound of formula (IA):



(IA)

in which P and P^1 are as defined above, and there after in any order:

- optionally reducing the compound (IA)
- removing any protecting groups.

2. A process according to claim 1 in which R is CH=CH.

3. A process according to claim 1 or 2 in which R^1 and R^2 are both hydrogen.

4. A process according to any one of claims 1 to 3 in which P is TBDMS and P^1 is TMS.

5. A process according to any one of claims 1 to 4 in which hydrogenation of the triple bond of the compound of formula (IA) is carried out using Lindlar hydrogenation.

6. A process according to any one of claims 1 to 4 in which reduction of the cyclopentanone of the compound of formula (IA) is carried out using K-selectride.

7. A compound of formula (I) prepared according to the process of claims 1 to 6.

DATED THIS 5TH DAY OF MARCH, 1998.

(MRS. A.V.NATHAN).
AGENT FOR THE APPLICANT.

Abstract

The invention relates to novel process for the preparation of prostaglandin compounds which are useful as medicaments.